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Research Article

Buprenorphine Half-Life - Further Considerations

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Abstract

Objective: We evaluated published studies on the half-life of sublingually administered buprenorphine to determine if the values reported, and promulgated, in medical reference documents are supported by those data.

Design: We analyzed, by regression analysis, a frequently referenced pharmacokinetic study on the elimination of sublingually administered buprenorphine.

Results: Buprenorphine appears to follow a three-compartment distribution/elimination process. The half-lives are: Alpha: 1.4 hours, Beta: 4.6 hours, Gamma: 16.5 hours. The predominant portion of the elimination occurs in the alpha and beta phases, but the gamma phase (sometimes called the "terminal" phase) which accounts for a minor mass of drug, appears to be closer to the values (24-69 hours) reported in medical reference documents.

Conclusions: Many clinicians who treat patients with opioid use disorder (OUD) have observed that, given the option, the majority of patients prescribed buprenorphine choose to split their daily doses into 2 or 3 portions in order to reduce withdrawal symptoms that may occur towards the end of that dosing period. We conclude that the "clinical", or effective, half-life of sublingually administered buprenorphine is much lower than that promulgated in most medical reference documents.

Keywords: Buprenorphine; Half-life; Opioids; Opioid Use Disorder; OUD; Pharmacokinetics

Abbreviations

OTP: Opioid Treatment Program; OBOT: Outpatient Based Opioid Treatment; OUD: Opioid Use Disorder; SAMHSA: US Substance Abuse and Mental Health Services Administration; IV: Intravenous; IM: Intramuscular; PK: Pharmacokinetics; ng: nanogram; mg: milligram; TI: Therapeutic Index; LD50: Dose That Causes a Fatality Rate of 50%.

Introduction

The opioid crisis is a global issue, and a US government document [1] provides an excellent overview of the opioid epidemic. Buprenorphine and methadone are used world-wide to treat opioid use disorders (OUD), besides being effective analgesics. But when considering these drugs for treating OUD, it is crucial to understand their effective half-lives. Common understanding, and the widely promulgated medical reference literature, hold that the half-life of buprenorphine, varies from 24 to 69 hours [2-4], comparable to that of methadone. A document called TIP 63 [5]: Medications for Opioid Use Disorder, published by the US Substance Abuse and Mental Health Services Administration (SAMHSA) quoted those references in both the original and revised versions.

However, after 6 years of treating patients with OUD, one author (DMS), has become suspicious that the clinical, or "effective", half-life of buprenorphine is significantly lower than reported. This conclusion is based on his experience working as a medical director or provider in both Opioid Treatment Programs (OTP) and Outpatient Based Opioid Treatment (OBOT) programs, and from discussions with similar practitioners at addiction medicine conferences. The former is a dispensing program and the latter a prescribing program for (theoretically) more stable, compliant patients. In the OTP full dosing is given on site each morning until the patient earns "take-homes", the number increasing as stability and reliability in

the program increases. Most OTP patients (when queried) reveal that they rarely take their home medication in one dose. The OBOT patients invariably split their daily dose when prescribed more than 8 mg daily.

This article represents an investigation into that puzzling clinical observation. While some of the preference to split the dose can certainly be attributed to the habitual-use mind set of opioid abusers, the practice seems too common for such a simplistic explanation. Anecdotally, it has been observed that requested dose increases can often be limited by better scheduling of the divided doses, timed to interdict the onset of early withdrawal symptoms, which may be mild, but which may cause anxiety or interfere with sleep.

We may not convince the reader of the reasons that patients split their doses, but we hope, in the following analysis, to provide compelling evidence that the clinical half-life of buprenorphine is significantly lower than commonly held.

Review

There appear to be inconsistencies in the early literature regarding the half-life of buprenorphine. In one of those early studies, Bullingham., *et al*. [6] administered buprenorphine intravenously (IV) and intramuscular (IM) for post-operative analgesia, in total doses up to 0.6 mg, and measured plasma levels for 3 hours. After ~20 minutes the elimination curves for IM and IV administration were congruent, as expected. Their conclusion was that "The terminal $t_{1/2}$ (half-life) was *slow*, approximately 3 hr". More specifically, they determined that the plasma elimination was "tri-exponential" with the alpha, beta, and gamma half-lives being 2.2 min, 18.7 min, and 183.6 min, respectively.

A study [7] conducted on behalf of Reckitt Benckiser, the marketer of Subutex® and Suboxone ®, reported what they called a "terminal" half-life of 26 hours (denoted with the subscript "z") that was derived by linear regression over the "terminal" phase. Visual inspection of their figures plotting plasma concentration versus time show half-lives in plasma of no more than 4 hours. The authors stated that their analytical method was sufficiently sensitive to quantify plasma buprenorphine concentrations after a single 2 mg dose, but they were not able to calculate a half-life for that dose, stating that "… reliable estimation of $t_{1/2z}$ was possible in only a few subjects at the 2 mg dose level".

Two publications by Harris., *et al*. [8,9] provide additional data helpful in estimating the plasma half-life of buprenorphine. Figure 4 in the 2000 article [8] shows log-linear presentations of mean plasma buprenorphine concentrations for 8 mg buprenorphine, with and without naloxone. The 3 graphs for buprenorphine show almost perfect congruence, as expected.

The peak concentration for buprenorphine in their study was 8 to 9 ng/ml and occurred at approximately 1 hour after administration. At 3 hours after administration, the plasma levels were down to half that value, yielding a plasma $t_{1/2}$ of ~3 hours, consistent with the original conclusion of Bullingham [6]. However, in Table 1 of the 2000 Harris paper [8] they reported half-lives of 19 to 23 hours. In the 2004 paper [9] they again reported PK data on sublingually administered buprenorphine, but this time the fluctuating terminal values "precluded calculation of valid half-lives".

Figure 1: Adapted (with permission) from Harris [9] showing a graph of the plasma concentrations versus time of 4 different formulations of buprenorphine. Doses are labeled by buprenorphine (B) dose in mg, and naloxone (N) dose in mg.

Review of Figure 1 might lead one to estimate visually a half-life of no more than 4 hours, and even that estimate might be generous. Take, for instance, the preparation of B16/N4 (16 mg buprenorphine/4 mg naloxone) which peaks at 5 ng/ml. By 3 hours after administration the concentration had fallen to just over 2 mg, consistent with a half-life of no more than that. Again, these data are consistent with the PK curves shown by Harris (2000), although those data were graphed in log-linear form and this figure is linear-linear. The shape of the curve also suggests a multi-compartmental disposition system, which we felt would justify further analysis.

Method and Results

Burkett [10] contends it is possible to obtain a "ballpark" estimate of the half-life of the drug by observing the graph of plasma concentration versus time, but a more precise calculation of the elimination rate constants for various compartments, and thereby the disposition half-live(s), requires a mathematical regression analysis of the plasma-time curve.

Since Kuhlman is the author that was referenced in TIP63, and who provides the most often quoted data on the PK of buprenorphine, we felt it prudent to inspect that author's raw data and analyze them further, in order to better understand how the conclusions were reached. As best we can determine, the original data, from which all subsequent analyses are derived are presented in Table 1 of their 1996 paper [2]. We put the tabular data from the continuation of Table 1, for patients administered 4 mg sublingual buprenorphine, into an Excel® spreadsheet and graphed it.

The authors reported timed plasma buprenorphine concentration data, measured from 0.04 hours to 96 hours. The maximum plasma values (C_{max})varied from 1.93 ng/ml to 7.19 ng/ml, reaching those peaks in ½ to 1 hour. The data for 6 patients are shown in figure 2.

Figure 2: Data for 6 individual patients plotted from t=0 to t=10 hours. Plotted from data in the continuation of Table 1, on page 371 of Kuhlman [2].

For completeness, we have also plotted in figure 3 the concentration data up to 48 hours. Since the clinical effect requires entry into the brain, which action is proportional to plasma concentration, it seems unlikely that the clinical or effective $t_{1/2}$ is as long as 24 to 48 hours.

Figure 3: Plasma concentration of the 6 individual patients [2] carried out to 48 hours post sublingual administration of 4 mg buprenorphine.

Gross inspection of the time course (in either figure) looks remarkably similar to the graphic data in the two Harris articles [8,9]. The time to decrease from C_{max} to ½ C_{max} (plasma $t_{1/2}$) for no patient exceeded 3 hours.

The slope of various parts of the curves also appeared to be consistent with first order elimination kinetics but to verify this hypothesis we graphed the natural logarithm (Ln) of the mean values for the 6 patients administered 4 mg sublingual buprenorphine, and performed a regression analysis, carried out to several time points. The numbers are slightly different from Kuhlman because they included an obvious outlier in patient C at 0.17 minutes.

Figure 4: Ln of mean values and regression lines from Cmax to 4 hours and from 4 to 10 hours. The points marked with an open circle are the Ln of the mean values listed in the referenced Kuhlman article. The points marked with the X solid show the regression line from the peak to 4 hours. The red line shows the regression line from 4 to 10 hours.

The 4-hour regression line (alpha compartment) is: Y = 1.515 - 0.508X
(R^2 = 0.996) P= 0.0001 95% confidence limits of k_e = {0.448,0.567}
So $t_{1/2}$ = 0.693/k_e which yields $t_{1/2}$ = 1.36 hours 95% confidence limits {1.22,1.55}

The regression from 4 to 10 hours (beta compartment) is: Y = 0.090 – 0.151X
(R^2 = 0.977) P= 0.0015 95% confidence limits of k_e = {0.108, 0.193}
So $t_{1/2}$ = 0.693/k_e which yields $t_{1/2}$ = 4.59 hours {3.6, 6.42}

Figure 5: Regression analysis of Kuhlman data, from 10 h to 48 hours.

We also ran regressions of the Kuhlman data from 10 to 48 hours. The regression parameters for this line (gamma compartment) are:

Y = -0.885 – 0.042X R^2 = 0.84 P=0.01 95% confidence limits of k_e = {0.017, 0.068}
$t_{1/2}$ = 0.693/0.042 = 16.5 h 95% confidence = {10.2,40.8}

The terminology of alpha, beta, and gamma for these portions of the elimination curve follows the designations used by Bullingham [6], although the time intervals for sublingual administration are longer that those observed for IV administration. The intervals were chosen visually, but after analysis they show statistically significant fits to the data.

The different slopes of the 4h, 10h, and 48h lines most likely represent different compartments, or disposition "phases", as the drug moves among compartments until elimination from the body. The 48h slope might be called "terminal half-life", i.e. complete elimination of all drug from the body, although it is clear that the quantity of drug (AUC) under the portion of the elimination curve after 10 hours is small, viz. 2.5 logs smaller than the area from 0-10 hours.

Of note, Table III of Kuhlman shows various PK parameter for patients receiving 1.2 mg buprenorphine IV, and for the mean of the 6 patients. The mean k_e is reported to be 0.30, which would result in a $t_{1/2}$ = 2.31 h. (The number in the table is 3.21, which most likely represents a typographical transposition.) However, Table IV which presents individual and mean data for 4 mg sublingual dosing reports a mean k_e = 0.042, and a mean $t_{1/2}$ = 27.72 hours. (A recent report by Dong., *et al*. [11] using the same composite, non-compartmental analysis confirms half-lives from 22 to 39 hours.).

Thus, the data analyses in Kuhlman appear to conflict with their own data and the conclusions of Bullingham [6] and Harris [8,9]. Therein lies, what we believe to be the origin of the long half-life reported for sublingually administered buprenorphine.

Discussion

We have demonstrated that the commonly promulgated belief that buprenorphine has a long half-life may be clinically misleading. By gross visual analysis of concentration-time graphs, and by graphing and mathematical analysis of raw data, we have shown that the plasma half-life of buprenorphine is on the order of 4 hours (or less), not 24 hours.

Although many pharmacologists de-emphasize $t_{1/2}$ as a primary PK parameter, half-life is still the PK parameter most often quoted in the clinical literature because it is relatively easy to compute, given plasma concentration versus time after an IV or rapidly absorbed dose of medication.

But it is apparent that part of the problem we faced in researching this study is terminology. One will find many adjectives that modify the term half-life, including plasma, terminal, terminal plasma, elimination, terminal elimination, peripheral, and often the term is used with no modifier at all. Even in the 1996 Kuhlman document [2] the terms "elimination half-life", "terminal half-life", and "plasma terminal elimination half-life" appear to be used interchangeably.

Wright and Boddy [12] in their paper, "All Half-Lives Are Wrong, But Some Half-Lives Are Useful", discuss the problems of measuring

half-life because of multi-compartment accumulation, movement of drug among the compartments, and elimination. The problem is further compounded because (in the human anyway) we can generally only measure drug concentration in one compartment - plasma. Indeed, that is reinforced in TIP 63: "Half-life: Rate of removal of a drug from the body. One half-life removes 50 percent from the plasma".

Sahin., *et al*. [13] sought to define the term "operational multi-dosing" half-life, which to a clinician is clinically significant. They state that the value reported for many drugs is not the relevant half-life, that "… the appropriate method for determining the relevant half-life has not been adequately discussed in the literature", and that "In a number of cases, well accepted and generally used approaches are just wrong".

We reiterate that our analysis is intended to be clinically applicable, but we do not attempt to establish the effective or therapeutic duration of buprenorphine (time between C_{mec} and $C_{max)}$, either as a single dose or in multiple dosing regimens. There are too many variables involved in that analysis, which are well beyond the scope of this paper. Such variables involve receptor binding affinity, saturation, and temporal relationships – which are all poorly understood in humans. For further discussion of these issues, the reader is referred to Greenwald [14] and Boas [15].

Figure 6: A plot of Cp versus Time for Multiple Oral Doses showing Cpmax and Cpmin Citation: https://www.boomer.org/c/p4/c15/c1502.php Used with permission.

Nevertheless, clinicians use reported half-lives when deciding on dosing regimens (Shargel[16], p 490). For instance, Figure 6 depicts a simplistic time course of a hypothetical drug plasma concentration and illustrates the main pharmacokinetic metrics of oral administrations every 6 hours. The elimination half-life is 4.6 h (k_e = 0.15). Cp_{max} is critical for considerations of acute toxicity and Cp_{min} is important for considerations of symptomatic relief, in the case of medication assisted treatment for OUD. In a clinical sense, Cp_{min} may also be referred to as MEC (minimal effective concentration).

But toxicity is not a consideration with buprenorphine, which has a wide TI (Therapeutic Index). The LD_{50} cannot be known in humans, but the lethal dose is extremely high in rats [17] reportedly over 90 mg/kg, which equates to an absurd dose in the average human! Reports on buprenorphine "related" deaths do not allow that determination because of combinations of multiple drug intake or limited data, but the risk of respiratory depression and overdose on buprenorphine, in the absence of concurrent central nervous system depressants, must be extremely low [18]. So, in theory, increasing the daily dose could assure that Cp_{min} is always maintained above MEC, and would not be dangerous, but would certainly not be cost effective and might even promote diversion.

Thus, the critical numbers for clinical dosing decisions are plasma half-life and MEC. Indeed, Bullingham [19], as early as 1981, noted that "… a major determinant of loading of the opiate receptor is likely to be the time during which plasma buprenorphine levels are sustained".

Once the receptors are saturated no additional benefit is gained from higher or more frequent dosing, but dosing intervals that are too large can result in wide swings between C_{max} and C_{min}, producing levels below the MEC, causing withdrawal symptoms and cravings, i.e. the duration of effect is shorter than the dosing interval.

But plasma concentration is the primary factor that controls diffusion of the drug into the brain. And plasma concentration versus time analyses are the only data which have been used to report what is generically called drug half-life, and which is often used to make clinical dosing decisions, including dosing regimens and dosing change decisions.

The reportedly long half-life appears to represent the time required to eliminate half the administered dose of the drug by calculating AUC (Area Under the Curve) to infinity, which is a non-compartmental method for determining half-life [16,20]. Using the data in table IV of Kuhlman and the formula k_e = Cl/ Vd one obtains the

almost identical numbers in the column for k_e, and corresponding half-lives. (There is one exception: The value for mean $t_{1/2}$ would be 22.23 h, not 27.72 h.).

The problem with this method, however, one author [21] contends that "Terminal plasma half-life is the time required to divide the plasma concentration by two after reaching pseudo-equilibrium, and not the time required to eliminate half the administered dose". The time to pseudo-equilibrium is dependent upon the formulation and the route of administration, but in the case of a sublingual formulation, even if one includes the time to reach C_{max} (30 to 60 minutes (Figure 2) the plasma half-life cannot be any more than 4 hours, even considering lipid and protein binding.

AUC is a measure of the extent of total systemic exposure to a drug. AUC and C_{max} are often used in bioequivalence comparisons and are clinically useful in considering the amount of drug absorbed systemically, for therapeutic and/or toxicity considerations. But AUC cannot be used to determine the duration of drug clinical action (by any definition of that term), which can only be determined by clinical studies, and which are not purely mathematical exercises.

MEC is directly dependent on patient-specific parameters such as volume of distribution and clearance rate, which are in turn affected by patient health status, body mass index, blood volume, metabolism, pH, protein binding, renal and hepatic function, and third-space dynamics. Other considerations include receptor binding kinetics, but the temporal binding of buprenorphine to the mu (and other) opioid receptors is poorly understood in humans. These complexities can explain why patients require different dosing regimens to achieve relief from withdrawal symptoms.

But despite all the variables affecting clinical efficacy, there is little argument that the clinically relevant, "effective", half-life must, in some way, correlate with the plasma levels, which, for the slower portions of the elimination curve are miniscule. To invoke any other association begs physiologic credulity.

Figure 7 is a frequency distribution of dosing in the OTP directed by one author (DMS), which, accounting for the variability among formulations of medication and the biological variability among patients, essentially confirms the dosing efficacy of Kuhlman [3] and the opinion of Greenwald [18], that there are limits to the scientific evidence available for determining appropriate doses of buprenorphine.

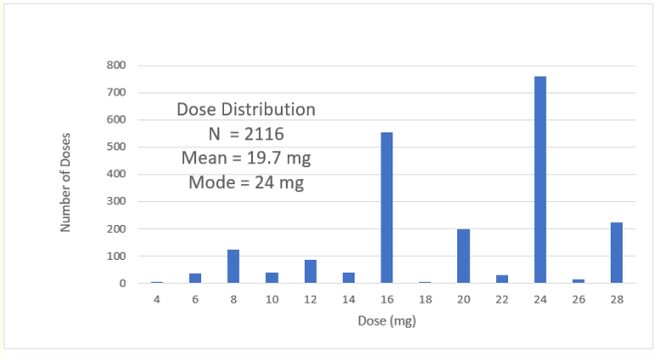

Figure 7: Frequency distribution of buprenorphine doses in a large Opioid Treatment Program directed by author DMS, for 2116 doses administered during the period 11/1/2019 – 11/31/2019. Except for "take-home" doses, the full dose is administered at the same time in the morning. All patients requiring more than 8 mg report dividing their take-home doses, as do all patients in that author's OBOT clinic.

Conclusions

We believe we have demonstrated that the commonly held belief that buprenorphine's half-life is 24 hours or longer (i.e. comparable to methadone) is clinically misleading, and that what is reported as "terminal" half life is not the relevant PK parameter.

Opioid abusers are sensitive to perceiving plasma concentration excursions below MEC. The withdrawal symptoms may be mild, but in these "delicate" patients even mild symptoms induce anxiety, interfere with sleep, and may trigger relapse. That relapse may drive the patient to use other addictive, and more dangerous, substances to mitigate the symptoms.

By gross visual analysis of concentration-time graphs, and by graphing and mathematical analysis of raw data, we have shown that the plasma half-life of buprenorphine is on the order of 4 hours, not 24 hours. Dosing regimens must be flexible enough to account for potential excursions below MEC and for biologic variability among patients.

The biggest limitation of this study is that, because we are using raw plasma data from a historical source, we are unable to directly correlate those levels of buprenorphine with clinical effect. However, it is indisputable that such effect is dependent upon binding of buprenorphine to the opioid receptors in the brain, and entry

across the "blood brain barrier" is directly related to plasma concentration of the drug. Therefore, any small mass of drug that is distributed in third spaces, and therefore contributes to the long "terminal" elimination, can have no contribution to the clinical action of the drug, unlike the actions of such drugs as antibiotics or chemotherapeutics.

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